IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No: 37945-0005

Applicant: Richard Anthony Godwin SMITH *et al.*

Serial No.: 09/214,913 Group Art Unit: 1644

Filing Date: March 16, 1999 Examiner: P. Huynh

Title: CONJUGATES OF SOLUBLE PEPTIDIC COMPOUNDS WITH MEMBRANE-BINDING AGENTS

DECLARATION OF DR. RICHARD ANTHONY GODWIN SMITH

I, Richard Anthony Godwin Smith, do hereby declare as follows:

1. I am the Chief Scientific Officer for Adprotech Ltd, and a co-inventor named on the captioned application.

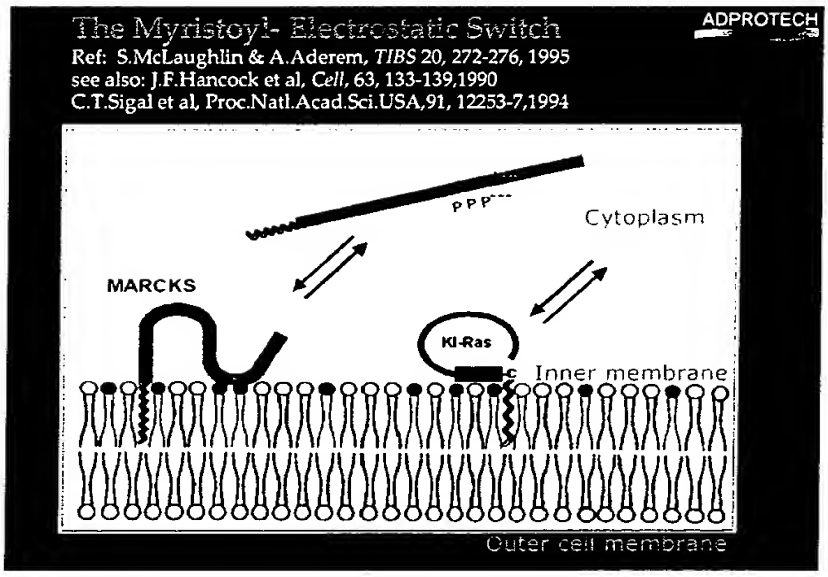
2. I received my doctorate in 1974 from Oxford University. My thesis was entitled "Photogenerated Labels for Biological Receptor Sites." I have been engaged in research in the fields of biochemistry, molecular biology and protein engineering for over 30 years. A copy of my *curriculum vitae* is attached at Tab 1.

3. I have reviewed the captioned application and the office actions issued by the examiner, including the final office action dated April 22, 2002 (Paper No. 17). I provide this declaration to explain the need satisfied by the present invention, how the present invention works, and the broad scope and applicability of the invention.

4. There is a need to direct therapeutic agents to sites within the body. There has been debate, however, whether true targeting is achievable in the complex molecular space of higher living organisms. In practice, the nature of what is to be delivered may be incompatible with delivery to the required site. For example, the delivery of potent cytotoxic drugs to tumors can be difficult if tumor-specific targets are present only at low levels on accessible tumors. Applicants' invention, however, does not suffer from these limitations.

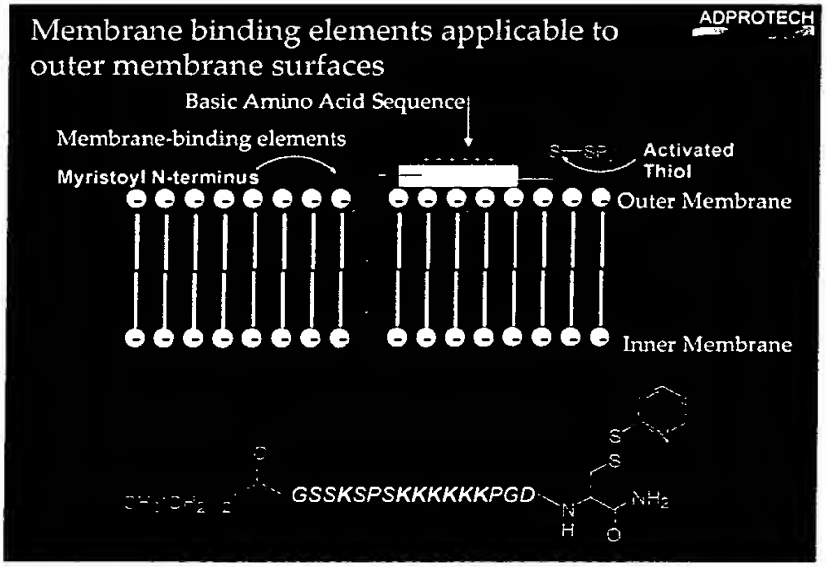
5. In 1995, McLaughlin and Aderem published their findings on the "Myristoyl-Electrostatic Switch." This mechanism allows proteins to associate with a cell

membrane through both hydrophobic and electrostatic interactions, and then to be released from the inner cell membrane by the phosphorylation of serines, which neutralizes a nearby positively charged region. The resulting "switch" in charge within a localized region of the protein sequence neutralizes the electrostatic component of the interaction and allows translocation of the protein from the membrane to the cytoplasm. Proteins such as MARCKS (Myristoylated alanine-rich C kinase substrate), K-Ras, Scr (Sigal *et al.*) have this ability. A key point is that the proteins are released into the cytoplasm, meaning that the proteins are released from the inner cell membrane. This is depicted schematically below. Note that the myristoyl region (orange) intercalates itself into the lipid bilayer in the inner cell membrane. The positively charged amino acids (+) can interact with negatively-charged phospholipids (blue). When the serine residues are phosporylated (P^-), their negative charge neutralizes the net positive charge of the region. Once the electrostatic interaction is broken, the myristoyl region also dissociates from the lipid bilayer, allowing the protein to freely enter the cytoplasm.



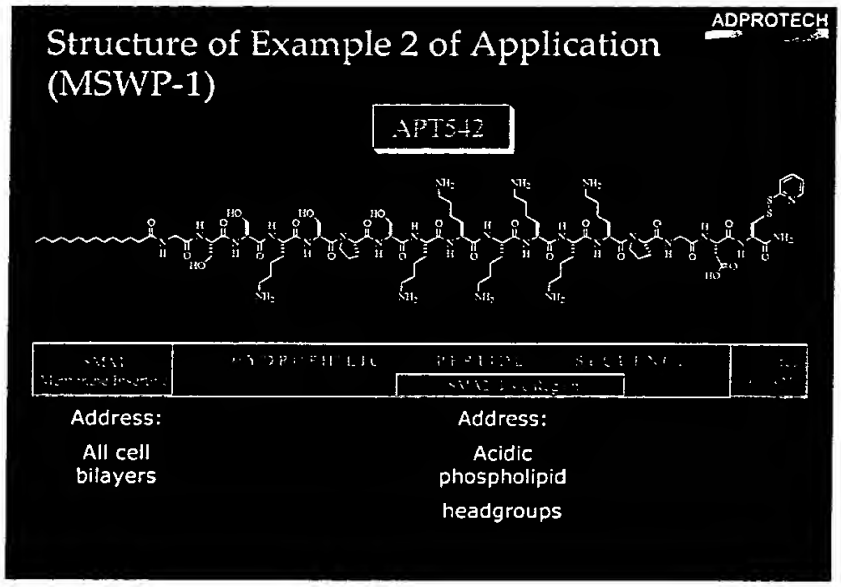
6. The present invention was inspired by the myristoyl-electrostatic switch, and marks an adaptation of the approach to binding at the outer membrane, which had never previously been performed. Below is depicted a schematic of exemplary binding elements according to the invention. This schematic depicts a hydrophilic binding element in yellow and a lipophilic (for example, myristoyl) binding element in green. An activated

thiol moiety (S-Spy) is a linker that links the compound to be directed to the binding elements. The combined action of the hydrophilic region and the lipophilic region permit the binding elements and compound to be direced to outer membrane. Thus, each binding element acts as an 'address' and the approach can be referred to as "addressive localization." The molecule at the bottom of the above slide contains a myristoyl region, which is lipophilic and a polylysine region, which is hydrophilic and basic.

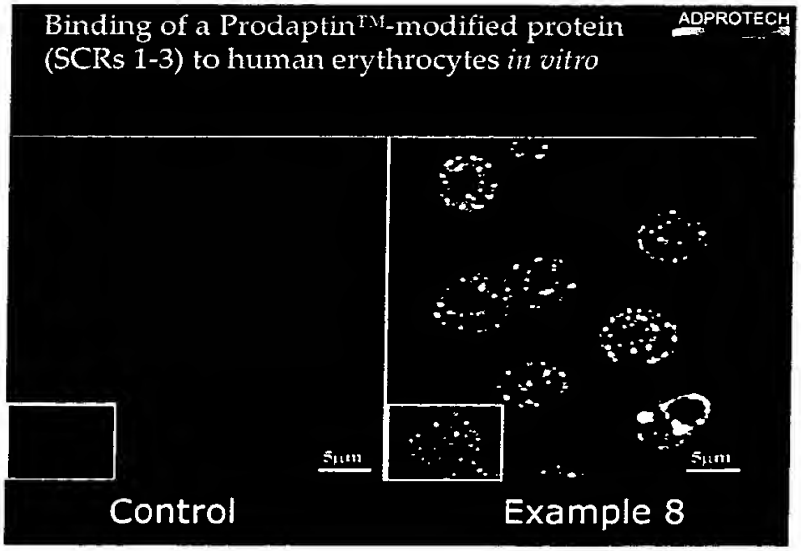


The combination of these type of elements forms a membrane localization reagent and is referred to commercially as Prodaptin™. An example is MSWP-1 (also referred to as "APT542").

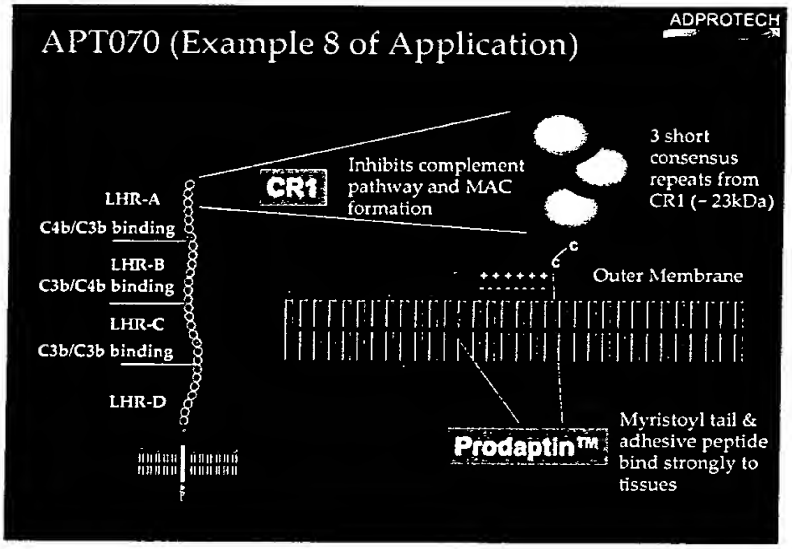
7. Example 2 of the application is schematically depicted below. This combination has a myristoyl lipophilic element (SMA1), which addresses cell bilayers, and a basic element of six lysine residues (SMA2), which addresses acidic heads of phospholipids. The two elements are bound with a linker, which allows the membrane localization reagent to be conjugated to the molecule to be addressively localized. Overall, the molecule is not hydrophobic, and is soluble.



8. Short Consensus Repeats (SCR) 1-3, which are part of Long Homologous Repeat A (LHR-A) of Complement Receptor 1 (CR-1), were linked to MSWP-1, which is depicted above. The preparation of this molecule is discussed at Example 8 of the captioned application. This molecule was then fluorescein labelled, and then contacted with human erythrocytes. See pages 55-57 of the captioned application. The below photographs dramatically show the increased binding of the Prodaptin™-modified SCR 1-3 as compared to an unmodified control.



9. The molecule described in Example 8 is depicted in greater detail below. This molecule comprises SCR1-3 of LHR-A of CR1 conjugated to Prodaptin™, as noted above. When linked to SCR1-3, Prodaptin™ confers high affinity cell surface binding that enables SCR1-3 to act in its natural environment close to the surface of the cell and control the progression of the complement cascade and MAC (membrane attack complex) formation. The left-hand portion of the slide depicts LHRs A-D of CR1, which contain SCR 1-3 at the outermost portion of the chain. The right-hand portion of the slide shows SCR 1-3 as linked to Prodaptin™ according to the present invention. The whole molecule was named test compound "APT070."



10. The activity of APT070 was assessed and measured in a number of biological assays. One assay was an anti-hemolytic assay, which sensitizes red blood cells (normally sheep) with an antibody. The red blood cells can then be lysed with serum complement from various species under standard controlled conditions. If the test compound has anti-complement activity, the erythrocytes will be protected from lysis. The inhibition of hemoglobin release by the test compound is measured spectrophotometrically. The anti-hemolytic activity of a number of compounds has been tested. These showed that the activity of APT070, having a relative potency of 133, was significantly more potent than SCR1-3 alone having a potency of 1. Further, the potency of modifications using single membrane binding elements was shown to be less than the combination of the two

used in APT070. This demonstrated that a combination of two or more membrane-binding elements was needed for optimal activity.

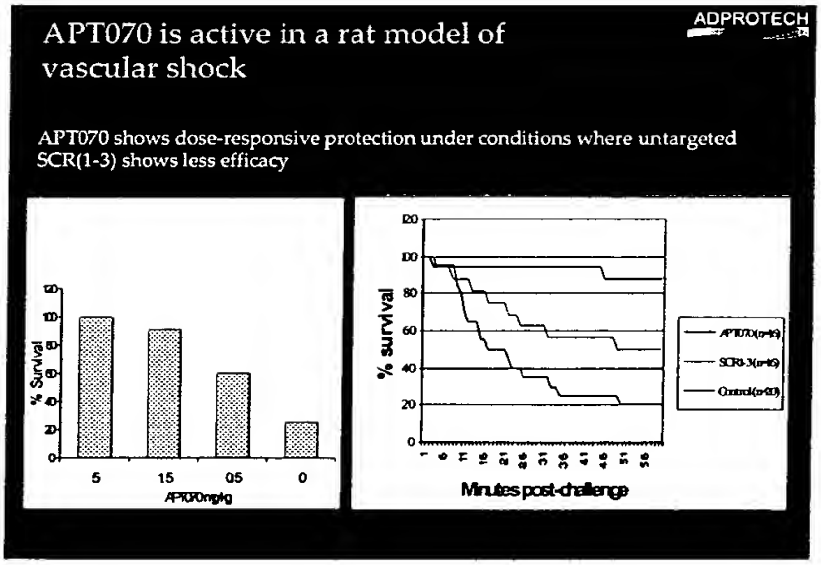
ADPROTECH

At least two membrane-binding elements are needed for potent anti-hemolytic activity:

Half-maximal inhibitory concentrations (IH50%) of unmodified and membrane-targeted complement inhibitor constructs

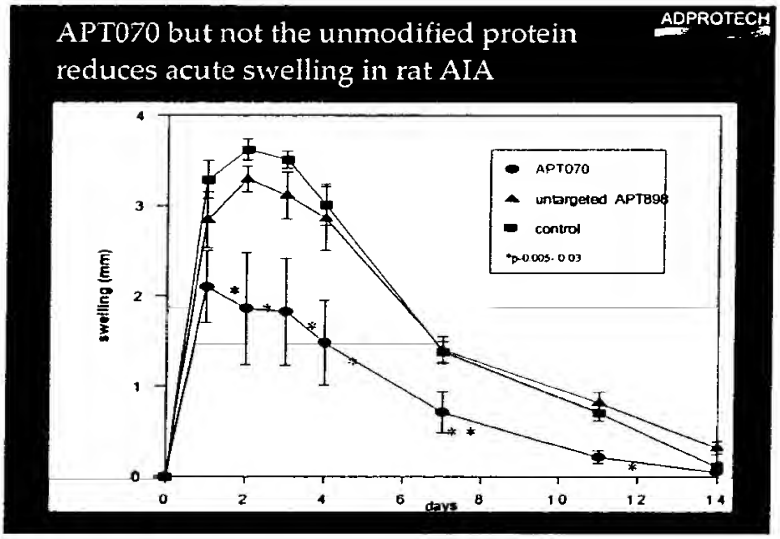
Construct	IH50% (nM)	Rel Potency
SCR1-3 of human CR1	20	1.0
SCR1-3cys	20	1.0
APT542	~800	<0.02
SCR1-3-cys-S-S-CH2CH2NH-C(O)-$(CH_2)_{12}CH_3$	22	0.9
SCR1-3DGPKKKKKKSPSKSSGC	25	0.8
SCR1-3cys-S-S-CDGPKKKKKKSPSKSSG-NH-C(O)-$(CH_2)_6CH_3$	6	3.3
SCR1-3-APT542 (APT070)	0.15	133

11. APT070 also was tested in a rat vascular shock model. This model assays the ability of a compound to protect a compromised rat from the acute effects of complement activation. APT070 was shown to provide dose responsive protection under conditions where a control, unmodified version of SCR1-3, was not as effective.



12. Complement and the MAC have been implicated in rheumatoid arthritis. In a study using an antigen-induced model of rheumatoid arthritis (AIA) in rats, the use of APT070 was shown to be effective at reducing acute swelling. In the AIA model, arthritis in a joint is initiated locally by an antigen-antibody interaction and hence classical pathway complement activation. The histology of such a model is similar to rheumatoid arthritis (RA) with synovial proliferation, pannus and erosion of the joint. In addition, within the joint there is the presence of immune complexes in RA synovial fluid with evidence of complement consumption.

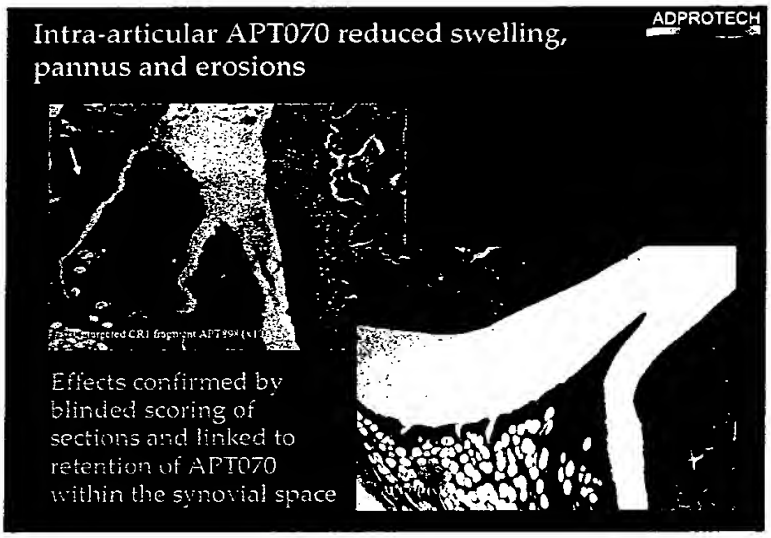
APT070 was assessed in the AIA model along with suitable controls, including an unaddressed peptide. This unaddressed peptide contained the SCR1-3 active peptide without binding elements (referred to as APT898).



The results showed that APT070 significantly reduced the acute swelling of the joint in this model. SCR1-3 alone did not significantly reduce the swelling.

13. The difference between the membrane binding form SCR1-3 (APT070) and the unmodified soluble SCR1-3 (APT898) was clearly seen in a blinded scoring of sections through the joint. Histology was carried out on sections taken from the joints of the various animals treated with the different therapeutic agents. The joint treated with APT070 not only had reduced swelling but also reduced pannus (the replacement of cartilage by a layer of vascular soft tissue) and erosion in the joint. This compared with the

joint treated with SCR1-3 without membrane binding capability, which showed evidence of pannus and erosion, in addition to swelling.

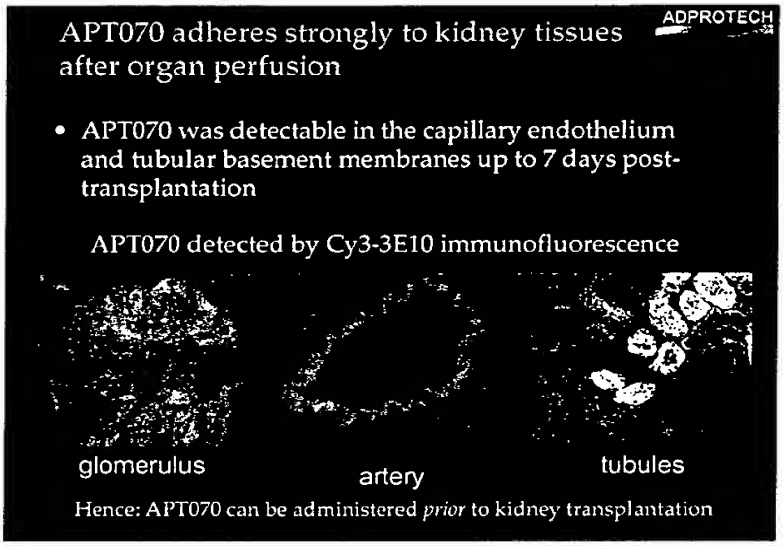


These and other data demonstrate that APT070 could have a role in the treatment of rheumatoid arthritis. The Prodaptin™ modification is key to such a role because it increases the anti-complement potency of the therapeutic agent and enables its retention within the joint.

14. APT070 also may by useful in the prevention of transplantation ischemic reperfusion injury. There is a substantial body of evidence that indicates that ischemic reperfusion damage is linked to complement activation. Ischemic reperfusion leads to acute tubular necrosis (ATN) in non-living donor kidney transplants, which in turn leads to both acute and chronic rejection. In addition, there is evidence that delayed graft function (DGF) due to ischemic reperfusion injury results in greater number of transplant rejections. Preventing DGF and ATN using APT070 may reduce the incidence of transplant rejection and also significantly increase the number of organs that are available for transplantation.

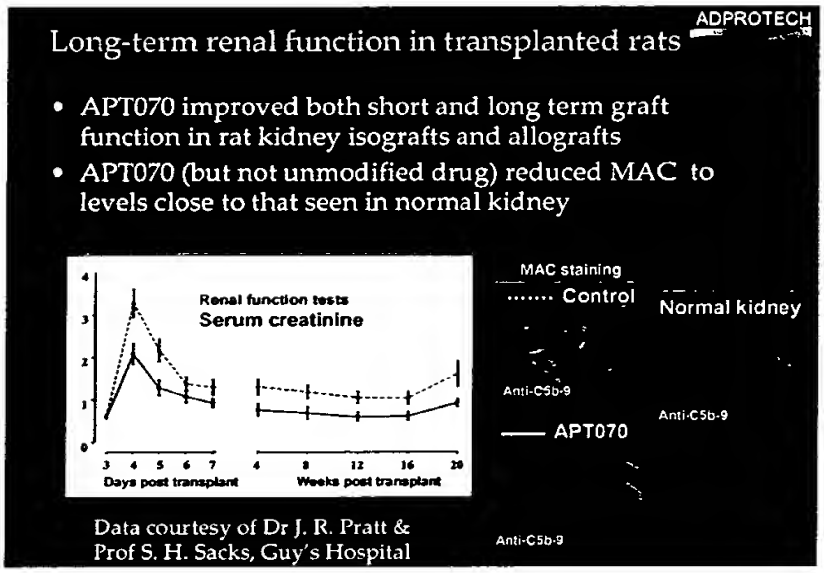
Studies have shown that if an organ, such as a kidney, is perfused with a solution of APT070, APT070 binds to the tissue in the kidney. In one study, a kidney was removed from a rat and perfused with APT070. A histological study of the kidney was undertaken. The presence of APT070 in the kidney sections was detected by Cy3-3E10 immunofluorescence (3E10 is a monoclonal antibody directed against SCR1-3). APT070

was shown to be present not only lining the arteries of the kidney, but also in the glomerulus and tubules.



In another study, kidneys were transplanted from a donor animal to a recipient animal. The transplanted kidneys were later removed after various time points and a histological examination performed. APT070 was shown to be still present in the kidney seven days post-transplantation. Hence, the perfusion of a kidney with a solution of APT070, prior to transplantation but once removed from the donor, can have a beneficial effect on the transplant without the need to infuse the drug prior to its removal from the donor. This may lead to a greater survival of the transplant and a reduction in transplant rejection, but at the same time have a lower drug requirement and better compliance.

A third study was conducted in which a kidney was removed from a donor animal, perfused with a solution of APT070 and then transplanted into a recipient. The renal function of the recipient animal was then monitored over a period of time to study the effect of the perfusion of APT070 and long-term survival of the graft.



The serum creatinine level of recipient animals was shown to be lower (and close to normal) following treatment with APT070 than in control animals. This indicated that the kidney was functioning better after perfusion with APT070. The study showed that both short and long term graft function in kidney isografts and allografts was improved in those organs perfused with APT070 prior to transplantation as compared to control kidneys. Further, histological examination of the kidneys showed that those treated with APT070 but not unmodified SCR1-3 had reduced levels of MAC. These levels were similar to those measured in normal kidneys.

15. APT070 has undergone a number of toxicological tests in animals, in which it has been shown to be safe. These are summarized below

- Ascending single-dose studies performed in rats;
- Daily 14-day repeat dosing up to 30mg/kg in rats and marmosets;
- No Adverse Effect Dose Level (NAEDL) is greater than 30mg/kg/day in marmosets;
- Certain rat strains showed short-lived and reversible peripheral edema at greater than 10mg/kg, but this was not seen in marmosets;
- Genotoxicity assays (*i.e.*, Ames test mouse lymphoma assay and rat bone marrow micronucleus test) all negative;
- No acute cardiovascular effects in rats up to 30mg/kg; and
- No local irritancy in the rat knee when administered intra-articularly at 0.8mg/joint.

16. The combination of Prodaptin™ with SCR1-3 is an exemplary embodiment of our invention. Different molecules to be localized can be linked by different linkers to different binding elements in types and numbers as taught in the captioned application. These can achieve similarly impressive results. What is important is that there be a combination of at least one lipophilic binding element with at least one hydrophilic binding element to addressively localize a given molecule to the outer membrane of a cell.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

12 DECEMBER 2002
Date

Richard Anthony Godwin Smith

BRIEF *CURRICULUM VITAE*

Richard Anthony Godwin Smith

Born: 4 April 1949, Stroud, England - British Citizen
Contact: Tel (44) (0) 1799 532530
Fax: (44) (0) 1799 532543
Email: r.a.smith@adpro.co.uk

Education:	Keble College, Oxford University	1967-1973
	Batchelor of Arts	- 1970
	Part II Honours (Chemistry)	- 1971
	Thesis: Fluorinated triose phosphates	
	European Molecular Biology Organization training course (Cambridge University)	- 1971
	Doctor of Philosophy (Oxford University)	- 1974
	Thesis: Photogenerated labels for biological receptor sites	
Employment:	Demonstrator in Organic Chemistry, Oxford University	1971-1972
	Beecham Pharmaceuticals Research Division	1974-1988
	- enzymologist	
	- senior scientist, fibrinolysis research	
	- chief biochemist, thrombosis project	
	- manager, modified proteins, biotechnology dept	
	SmithKline Beecham plc, biopharmaceutical R&D	1989-1996
	- director, Protein Chemistry	
	SmithKline Beecham plc, molecular screening technologies	1996-1997
	- director. Therapeutic Proteins	
	Adprotech Ltd, co-founder & chief scientific officer	1997-

Scientific achievements:

- novel penicillin transformation processes	1974-1976
- mechanistic studies on clavulanic acid	1976
(----→ antibiotic 'Augmentin')	
- acyl-enzyme approach to thrombolytic therapy	1975-1980
(----→ thrombolytic 'Eminase')	
- structural studies on fibrinolytic proteins	1987- 1996
- development of soluble CR1 as a therapeutic agent	1989-1994
- structure of IL-4 & fibronectin binding proteins	1992-1994
- membrane addressins & their therapeutic applications	1996- present
- development of novel inhibitors of complement activation	1997- present
- development of C3d-based immune adjuvants	1997- present

(Scientific publications: see below)

Prizes & awards: biochemistry prize (Oxford 1969), Queen's Award for Technological Achievement (1991), Prix Galien (1991)

Scientific interests: protein engineering, integrative molecular biology of adhesion, hemostasis/fibrinolysis, complement activation and inflammation, vaccine development

Publications

This is not a comprehensive list of publications. It is a selection of higher-impact papers designed to illustrate areas of past and present scientific interest and expertise.

1. Photoaffinity Labelling, General Protein Chemistry and Protein Engineering

Smith RAG, Knowles J R. Aryldiazirines: potential reagents for photolabeling biological receptor sites. **J Amer Chem Soc** 1973 95 5072-5073

Smith RAG, Knowles J R. The utility of photoaffinity labels as mapping reagents: a study of sub-populations of a specific rabbit antibody by using structurally related photoaffinity reagents. **Biochemical J** 1974 141 51-56

Smith RAG, Knowles J R. The preparation and photolysis of 3-aryl, 3-H diazirines. **J Chem Soc** 1975 (Perkin Trans.II) 686-694

Significance: these papers are the first describing the use of diazirines as photolabels and also outline photoaffinity labelling methods since widely applied.

Garman A J, Smith RAG. The chemical modification of proteins (review). **Royal Society of Chemistry Specialist Periodical Reports,** Amino Acids, Peptides and Proteins 1982 13 70-131 Also reviewed in vols 14-16 of this series (1983-5)

Smith RAG, Dewdney JM, Fears R, Poste G. Chemical derivatization of therapeutic proteins. (review). **Trends in Biotechnology** 1993 11 397-403

Dodd I, Smith RAG *et al* (6 authors). Isolation and folding of proteins containing the short consensus repeat motif from an *E.coli* overexpression system. **Perspectives in Protein Enginering and Complementary Technologies** (Mayflower Press 1995)

2. Enzyme Immobilisation

Smith RAG. Amphipathic enzyme-polymer conjugates. **Nature (London)** 1976 262 519-520

Smith RAG. The preparation and properties of amphipathic enzyme-polymer conjugates. **Biochemical J.** 1979 181 111-118

3. Fibrinolysis - General

Smith RAG, Green J, Kopper P H. The purification and properties of a fibrinolytic neutral metalloendopeptidase from *Streptococcus faecalis*. **Arch Biochem Biophys** 1980 202 629-638

Dupe R J, English P D, Smith RAG, Green J. The evaluation of plasmin and streptokinase activator complexes in a new rabbit model of venous thrombosis. **Thrombosis and Haemostasis** 1981 46 528-534.

English P D, Smith RAG, Dupe R J, Green J. The thrombolytic activity of streptokinase in the rabbit. **Thrombosis and Haemostasis** 1981 46 535-537

Garman, A J, Smith RAG. The binding of plasminogen to fibrin: evidence for plasminogen-bridging. **Thrombosis Research** 1982 27 311-320

Fears R, Hibbs MJ, Smith RAG. Kinetic studies on the interaction for streptokinase and other plasminogen activators with plasminogen and fibrin. **Biochemical J** 1985 229 555-558

Smith RAG. An active-site titrant for human tissue-type plasminogen activator. **Biochemical J** 1986 239 477-479

Dodd I, Mitchell DL, Chapman CG & Smith RAG. The use of bovine fibrin-streptokinase films for the determination of recombinant human plasminogen. **Biologicals** 1992 20 197-202.

Signficance: these studies contributed to the methodological basis for the development of a new generation of thrombolytic agents.

4. Acyl-Enzyme Thrombolytics and APSAC (anistreplase)

Smith RAG, Dupe R J, English P D, Green J. Fibinolysis with acyl-enzymes: a new approach to thrombolytic therapy. **Nature (London)** 1981 290 505-508

Smith RAG, Dupe R J, English P D, Green J. Acyl-Enzymes as thrombolytic agents in a rabbit model of venous thrombosis. **Thrombosis and Haemostasis** 1982 47 269-274

Staniforth, D H, Smith RAG, Hibbs M J. Streptokinase and anisoylated streptokinase.plasminogen complex: their action on haemostasis in human volunteers. **European J Clinical Pharmacology** 1983 24 751-756

Green J, Dupe R J, Smith RAG, Harris G S, English P D. Comparison of the hypotensive effects of streptokinase-human plasminogen activator complex and BRL26921 (p-anisoylated streptokinase.plasminogen activator complex) in the dog after high-dose bolus administration. **Thrombosis Research** 1984 36 29-36

Dupe R J, English P D, Smith RAG, Green J. Acyl-enzymes as thrombolytic agents in dog models of venous thrombosis and pulmonary embolism. **Thrombosis and Haemostasis** 1984 51 248-253

Dupe R J, Green J, Smith RAG. Acylated derivatives of streptokinase.plasminogen complex as thrombolytic agents in a dog model of aged venous thrombosis. **Thrombosis and Haemostasis** 1985 53 56-59

Fears R, Green J, Smith RAG, Walker P. Induction of a sustained fibrinolytic response to BRL26921 *in vitro*. **Thrombosis Research** 1985 38 251-260

Cassels R, Fears R, Smith RAG. The interaction of plasminogen activators and their acylated derivatives with fibrin and cyanogen bromide fragments of fibrinogen: relationship to fibrinolytic potency in vitro. **Biochemical J** 1987 247 395-400

Smith RAG. The non-exchange of streptokinase from anisoylated plasminogen.streptokinase activator complex and other acylated plasminogen activator complexes. **Drugs** 1987 33(3) 75-79

Hibbs M J, Fears R, Ferres H, Standring R, Smith RAG. Determination of the deacylation rate of p-anisoyl plasminogen.streptokinase activator complex (APSAC, Eminase) in human plasma, blood and clots. **Fibrinolysis** 1987 2 235-240

Smith RAG. Fibrinolysis with acyl-enzymes (review) in **Atheroma and Thrombosis** (ed V V Kakkar) Pitman Press London 1985 269-284

Green J, Harris G S, Smith RAG, Dupe R J. Acyl-enzymes: a novel class of thrombolytic agents (review) in **Thrombolysis: Biological and Therapeutic Properties of New Thrombolytic Agents** (ed D Collen et al) Churchill Livingston Edinburgh 1985 124-167

Significance: these papers describe the conception, pharmacology, pharmaceutical development and first clinical studies on the marketed thrombolytic agent anistreplase (Eminase).

5. Third Generation Thrombolytic Agents

Kalindjian S B, Smith RAG. Reagents for reversible coupling of proteins to the active centres of fibrinolytic enzymes. **Biochemical J.** 1987 248 409-413

Cassels R, Smith RAG. Preparation and properties of a conjugate of immunoglobulin G with the active centre of human tissue-type plasminogen activator. **Fibrinolysis** 1987 2 1889-195

Smith RAG, Esmail A F. Pharmacokinetic properties of a conjugate of tissue plasminogen activator linked through the active centre to human fibrinogen. **Fibrinolysis** 1988 2 (supp 1) 31 (abstract)

Ferres H, Smith RAG et al (7 authors). Synthesis and Fibrinolytic properties of a conjugate of urokinase with the active centre of human plasmin. **Fibrinolysis** 1988 2 (supp 1) 64 (abstract)

Robinson J H,.. Smith RAG *et al* (14 authors). A recombinant chimeric enzyme with a novel mechanism of action leading to greater potency and selectivity than tissue-type plasminogen activator. **Circulation** 1992 86 548-552

Wilson S,... Smith RAG *et al* (9 authors). The use of active central acylation to control the pharmacokinetic profile of a recombinant chimeric plasminogen activator. **Thrombosis and Haemostasis** 1993 70 984-986

Lijnen H R, Smith RAG, Collen D. Functional properties of p-anisoylated plasmin-staphylokinase complex. **Thrombosis and Haemostasis** 1993 70 326-331

Significance: these were further contributions to the design and evaluation of novel recombinant, engineered or other thrombolytic enzymes designed to combine the best features of the currently used agents .

6. Protein Structure Studies

Oswald R E, Bogusky M J, Bamberger M, Smith RAG, Dobson C M. Dynamics of the multidomain fibrinolytic protein urokinase from two-dimensional NMR. **Nature (London)** 1989 337 579-582

Bogusky M J, Dobson C M, Smith RAG. Reversible independent unfolding of the domains of urokinase monitored by 1H NMR. **Biochemistry** 1989 28 6728-6735

Nowak U K, Li X, Teuten A J, Smith RAG, Dobson C M. NMR studies of the dynamics of the multidomain protein urokinase-type plasminogen activator. **Biochemistry** 1993 32, 298-309.

Li X, Smith RAG, Dobson C M. Sequential NMR assignments and secondary structure of the kringle from urokinase. **Biochemistry** 1992 31 9562-9571.

Li X, Bokman A M, Llinas M, Smith RAG, Dobson C M. Solution structure of the kringle domain from urokinase type plasminogen activator. **J. Mol Biol.** 1994 235 1548-1559

Teuten A J, Smith RAG, Dobson C M. Domain interactions in human plasminogen studied by proton NMR. **FEBS Letters** 1991 278 17-22

Redfield C,.. Smith RAG *et al* (7 authors). Secondary structure and topology of human interleukin 4 in solution. **Biochemistry** 1991 30 11029-11035

Smith L J, ..Smith RAG *et al* (7 authors). Human interleukin-4: the solution structure of a four-helix bundle protein. **J Mol Biol** 1992 224 899-904

Redfield C, Boyd J, Smith L J, Smith RAG, Dobson C M. Loop mobility in a four-helix bundle protein: 15-N NMR relaxation measurements on human interleukin-4. **Biochemistry** 1992 31 10431-10437

Redfield C, Smith RAG, Dobson C M. Structural characterisation of a highly-ordered 'molten globule' at low pH. **Nature Structural Biology** 1994 1 23-29

Significance: contributions to structural understanding of proteins of therapeutic importance.

7. Complement Research

Dupe R J, Smith RAG *et al* (8 authors). Utility of complement inhibition during myocardial reperfusion: pharmacology of soluble complement receptor 1. **Thrombosis and Haemostasis** 1991 65 (6) 695 (abstract).

Gibb A L, Freeman A M, Smith RAG, Sim E. The interaction of soluble human complement receptor type 1 (sCR1, BRL55730) with human complement component C4. **Biochimica et Biophysica Acta** 1993 1180 313-320

Dodd I,...Smith RAG et al (9 authors). Overexpression in *Escherichia coli*, folding, purification and physicochemical characterisation of the first three short consensus repeat modules of human complement receptor Type-1. **Protein Expression & Purification** 1995 6 727-736

Mossakowska D, Dodd I, Pindar W, Smith RAG. Structure-activity relationships within the N-terminal short consensus repeats (SCR) of human CR1 (C3b/C4b receptor). **Eur J Immunol.** 1999 29 1955-1965

Pratt JR.....Smith RAG et al (5 authors). Effects of complement inhibition with soluble complement receptort-1 on vascular injury and inflammation during renal allograft rejection in the rat. **Am.J.Pathol.** 1996 149 2055-2066

Bright JR..Smith RAG et al (6 authors). Complement C4 structure. **Perspectives on Protein Engineering** 1993 3 p 6

Dong J.....Smith RAG et al (5 authors). Strategies for targeting complement inhibitors in ischaemia/reperfusion injury **Mol. Immunol.** 1999 36 957-963

Linton SM....Smith RAG et al (6 authors). Therapeutic efficacy of a novel membrane-targeted complement regulator in antigen-induced arthritis in the rat **Arthritis & Rheumatism** 2000 43 2590-2597

Smith GP & Smith RAG Membrane-targeted complement inhibitors **Mol.Immunol,** 2001 38 249-255 *(review)*

Signficance: engineering and evaluation of complement proteins, two of which have entered clinical trials

8.Science Management

Dewdney JM, Smith RAG Putting a new spin on R&D assets in the pharmaceutical industry. **Drug Discovery Today** 1998 3 353-354 *(editorial)*